Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

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Summary Recommendations
Remdesivir is the only drug that is approved by the Food and Drug Administration for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. For more information on these antiviral agents, see Table 2f.
Remdesivir
• See Therapeutic Management of Hospitalized Adults with COVID-19 for recommendations on using remdesivir for the treatment of COVID-19.
Ivermectin
• There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.
Interferons
• The Panel **recommends against** the use of **systemic interferon beta** for the treatment of hospitalized patients with COVID-19 **(AI)**. • The Panel **recommends against** the use of **interferon alfa** or **lambda** for the treatment of hospitalized patients with COVID-19, except in a clinical trial **(AIIa)**. • The Panel **recommends against** the use of **interferons** for the treatment of nonhospitalized patients with mild or moderate COVID-19, except in a clinical trial **(AIIa)**.
Nitazoxanide
• The Panel **recommends against** the use of **nitazoxanide** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.
Hydroxychloroquine or Chloroquine and/or Azithromycin
• The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** and/or **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIIa)**.
Lopinavir/Ritonavir and Other HIV Protease Inhibitors
• The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Antiviral Therapy

Because SARS-CoV-2 replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.[1] Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness

progresses to the hyperinflammatory state that can characterize the later stages of disease, including critical illness.[2] For this reason, it is necessary to understand the role of antiviral medications in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.

The following sections describe the underlying rationale for using different antiviral medications, provide the COVID-19 Treatment Guidelines Panel's recommendations for using these medications to treat COVID-19, and summarize the existing clinical trial data. Additional antiviral therapies will be added to this section of the Guidelines as new evidence emerges.

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Remdesivir

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Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro activity against SARS-CoV-2.[1] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2]

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies. See Table 2a for more information.

Data on the safety and efficacy of using remdesivir in combination with corticosteroids are primarily derived from observational studies, with some (but not all) of these studies suggesting that remdesivir plus dexamethasone provides a clinical benefit for patients with COVID-19.[3-5] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized trial. However, there are theoretical reasons that combination therapy may be beneficial for some patients with severe COVID-19. Remdesivir has also been studied in combination with other immunomodulators, including baricitinib[6] and tocilizumab.[7] See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on using remdesivir with or without immunomodulators in certain hospitalized patients.

Monitoring and Adverse Effects

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions.

Liver function tests and prothrombin time tests should be performed for all patients before they receive remdesivir, and these tests should be repeated during treatment as clinically indicated. Remdesivir may need to be discontinued if a patient's alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed.[8]

Considerations in Patients With Renal Insufficiency

Each 100 mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECD), and each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECD.[8] SBECD is a vehicle that is primarily eliminated through the kidneys. A patient with COVID-19 who receives a loading dose of remdesivir 200 mg would receive 6 g to 12 g of SBECD, depending on the formulation. This amount of SBECD is within the safety threshold for patients with normal renal function.[9] Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.

Because both remdesivir formulations contain SBECD, patients with an estimated glomerular filtration rate (eGFR) of <50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of <30 mL/min. The FDA product label does not recommend using remdesivir in patients with an eGFR of <30 mL/min due to a lack of data.[10] Renal function should be monitored before and during remdesivir treatment as clinically indicated.[8]

In 2 observational studies that evaluated the use of the solution formulation of remdesivir (not the reconstituted lyophilized powder formulation) in hospitalized patients with COVID-19, no significant differences were reported in the incidences of adverse effects or acute kidney injury between patients with an estimated creatinine clearance (CrCl) of <30 mL/min and those with an estimated CrCl of ≥30 mL/min.[11,12] In 1 study, 20 patients had an estimated CrCl of <30 mL/min and 115 had an estimated CrCl of ≥30 mL/min;[11] the other study included 40 patients who had an estimated CrCl of <30 mL/min and 307 who had an estimated CrCl of ≥30 mL/min.[12] These observational data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.

Drug-Drug Interactions

Currently, no clinical drug-drug interaction studies of remdesivir have been conducted. In vitro, remdesivir is a minor substrate of cytochrome P450 (CYP) 3A4 and a substrate of the drug transporters organic anion transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein 1 (MATE1).[8]

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020). Remdesivir is not expected to have any significant interactions with oseltamivir or baloxavir, according to information provided by Gilead Sciences (written communications, August and September 2020).

See Table 2f for more information.

Considerations in Pregnancy

Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from small studies and case reports are reassuring.[13] Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse effects.[14]

Considerations in Children

Remdesivir is available through an FDA EUA for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. There are insufficient data on the safety and efficacy of using remdesivir to treat COVID-19 in hospitalized pediatric patients aged <12 years or weighing <40 kg because these populations have not been evaluated in the clinical trials for remdesivir. The limited data from the compassionate use program and small case series suggest that remdesivir was well tolerated in children who met the EUA criteria, but the data on young infants and neonates are extremely limited.[15-19] A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov Identifier NCT04431453).

Clinical Trials

Several clinical trials that are evaluating the use of remdesivir for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.

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Table 2a. Remdesivir: Selected Clinical Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for RDV. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTT-1: Multinational, Placebo-Controlled, Double-Blind RCT of Remdesivir in Hospitalized Patients With COVID-19[1]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following criteria:
  • Pulmonary infiltrates
  • SpO_2 ≤94% on room air
  • Need for supplemental oxygen, high-flow oxygen, NIV, MV, or ECMO
Key Exclusion Criteria:
• ALT or AST >5 times ULN
• eGFR <30 mL/min
• Pregnancy or breastfeeding
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for up to 9 more days (n = 541)
• Placebo for up to 10 days (n = 521)
Primary Endpoint:
• Time to clinical recovery
Key Secondary Endpoints:
• Clinical status at Day 15, as measured by an OS
• Mortality by Day 29
• Occurrence of SAEs
	Participant Characteristics:
	• Mean age 58.9 years
	• 53.3% White, 21.3% Black, 12.7% Asian, 23.5% Hispanic/Latinx
	• 26.2% with 1 and 55.2% with ≥2 coexisting conditions
	• 13.0% not on oxygen; 41.0% on supplemental oxygen; 18.2% on high-flow oxygen or NIV; 26.8% on MV or ECMO
	• Median time from symptom onset to randomization was 9 days (IQR 6–12 days)
	• 21.6% in RDV arm and 24.4% in placebo arm received corticosteroids during the study
	Primary Outcomes:
	• RDV reduced time to recovery compared to placebo (10 days vs. 15 days; rate ratio for recovery 1.29; 95% CI, 1.12–1.49; $P < 0.001$).
	• Benefit of RDV was greatest in patients randomized during first 10 days after symptom onset and those who required supplemental oxygenation at enrollment.
	• No difference in time to recovery for patients on high-flow oxygen, NIV, MV, or ECMO at enrollment.
	Secondary Outcomes:
	• Patients in RDV arm were more likely to show clinical improvement at Day 15 (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$).
	• No difference between arms in mortality by Day 29.
	• Proportion of patients with SAEs was similar between arms (25% vs. 32%).
		Key Limitations:
		• Wide range of disease severity among patients, and study was not powered to detect differences within subgroups
		• Powered to detect differences in clinical improvement, not mortality
		• No data on longer-term morbidity
		Interpretation:
		• In patients with severe COVID-19, RDV reduced time to clinical recovery.
		• The benefit was most apparent in hospitalized patients who were receiving supplemental oxygen.
		• There was no observed benefit in those on high-flow oxygen, NIV, MV, or ECMO, but study was not powered to detect differences within subgroups.

Methods	Results	Limitations and Interpretation
DisCoVeRy: Open-Label, Adaptive RCT of Remdesivir in Hospitalized Patients With Moderate or Severe COVID-19 in Europe[2]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • Illness of any duration • SpO_2 ≤94% on room air or use of supplemental oxygen, high-flow oxygen devices, NIV, or MV **Key Exclusion Criteria:** • ALT or AST >5 times ULN • Severe chronic kidney disease **Interventions:** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 days (n = 429) • SOC (n = 428) **Primary Endpoint:** • Clinical status at Day 15, as measured by an OS **Key Secondary Endpoints:** • Mortality at Day 29 • Occurrence of SAEs	**Participant Characteristics:** • Median age 64 years; 70% men; 69% White • 74% with ≥1 coexisting condition • 40% received corticosteroids during the study • Median days from symptom onset to randomization was 9 days in both arms • 61% with moderate disease and 39% with severe disease **Primary Outcomes:** • No difference between arms in clinical status at Day 15 (OR 0.98; 95% CI, 0.77–1.25; *P* = 0.85). • A prespecified subgroup analysis based on duration of symptoms found no significant difference in clinical status between arms. **Secondary Outcomes:** • No difference in mortality between arms (8% in RDV arm vs. 9% in SOC arm). • No difference in the proportion of patients with SAEs between arms (33% in RDV arm vs. 31% in SOC arm; *P* = 0.48).	**Key Limitations:** • Open-label study • 440 participants in this study also enrolled in the Solidarity trial **Interpretation:** • There was no clinical benefit of RDV in hospitalized patients who were symptomatic for >7 days and who required supplemental oxygen.
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of Repurposed Drugs in Hospitalized Patients With COVID-19[3]		
Key Inclusion Criteria: • Aged ≥18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours **Interventions:** • RDV 200 mg IV on Day 0, then RDV 100 mg daily on Days 1–9 (n = 2,743) • Local SOC (n = 2,708) **Primary Endpoint:** • In-hospital mortality **Key Secondary Endpoint:** • Initiation of MV	**Participant Characteristics:** • 47% aged 50–69 years; 18% aged ≥70 years • 67% on supplemental oxygen and 9% on MV at entry • Rates of comorbidities were similar between arms • 48% in both arms received corticosteroids during the study **Primary Outcome:** • In-hospital mortality: 11.0% in RDV arm vs. 11.2% in SOC arm (rate ratio 0.95; 95% CI, 0.81–1.11) **Secondary Outcome:** • Initiation of MV: 10.8% in RDV arm vs. 10.5% in SOC arm	**Key Limitations:** • Open-label design limits ability to assess time to recovery as RDV may have been continued even if patient improved • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge **Interpretation:** • RDV did not decrease in-hospital mortality or the need for MV compared to SOC.

Methods	Results	Limitations and Interpretation
GS-US-540-5774 Study: Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared With Standard of Care in Hospitalized Patients With Moderate COVID-19[4]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• Pulmonary infiltrates
• SpO_2 >94% on room air
Key Exclusion Criteria:
• ALT or AST >5 times ULN
• CrCl <50 mL/min
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 9 days (n = 193)
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 4 days (n = 191)
• Local SOC (n = 200)
Primary Endpoint:
• Clinical status at Day 11, as measured by an OS
	Participant Characteristics:
	• Demographic and baseline disease characteristics similar across arms
	• Ranges for participant characteristics across the 3 arms:
	  • Median age 56–58 years
	  • Men: 60% to 63%
	  • 81% to 87% required no supplemental oxygen; 12% to 18% required low-flow oxygen; 1% required high-flow oxygen or NIV
	• Concomitant medication use in the 10-day RDV, 5-day RDV, and SOC arms:
	  • Steroids: 15%, 17%, 19%
	  • Tocilizumab: 1%, 1%, 5%
	  • HCQ/CQ: 11%, 8%, 45%
	  • LPV/RTV: 6%, 5%, 22%
	  • AZM: 21%, 18%, 31%
	• Median length of therapy was 6 days in 10-day RDV arm and 5 days in 5-day RDV arm
	Primary Outcomes:
	• 5-day RDV arm had significantly better clinical status at Day 11 than SOC arm (OR 1.65; 95% CI, 1.09–2.48; *P* = 0.02).
	• No difference in clinical status at Day 11 between 10-day RDV arm and SOC arm (*P* = 0.18).
		Key Limitations:
		• Open-label design may have affected decisions on concomitant medications (e.g., more patients in the SOC arm received AZM, HCQ or CQ, and LPV/RTV) and time of hospital discharge
		• No data on time to return to activity for discharged patients
		Interpretation:
		• Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better clinical status at Day 11 than those who received SOC.
		• There was no difference in the clinical status at Day 11 between patients who received 10 days of RDV and those who received SOC.

Methods	Results	Limitations and Interpretation
GS-US-540-5773 Study: Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared with Standard of Care in Hospitalized Patients With Moderate COVID-19[5]		

Key Inclusion Criteria:
• Laboratory-confirmed COVID-19
• Pulmonary infiltrates and SpO_2 ≤94% on room air or receipt of supplemental oxygen
Key Exclusion Criteria:
• Need for MV or ECMO
• Multiorgan failure
• ALT or AST >5 times ULN
• Estimated CrCl <50 mL/min
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 4 days (n = 200)
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 9 days (n = 197)
Primary Endpoint:
• Clinical status at Day 14, as measured by an OS
Key Secondary Endpoints:
• Time to clinical improvement
• Time to recovery
	Participant Characteristics:
	• Median age 61 years in 5-day arm vs. 62 years in 10-day arm
	• 60% were men in 5-day arm vs. 68% in 10-day arm
	• Oxygen requirements at baseline for the 5-day and 10-day arms:
	  • None: 17%, 11%
	  • Low-flow supplemental oxygen: 56%, 54%
	  • High-flow oxygen or NIV: 24%, 30%
	  • MV or ECMO: 2%, 5%
	• Patients in 10-day arm had worse baseline clinical status than those in 5-day arm (P = 0.02)
	Primary Outcome:
	• After adjusting for baseline clinical status, Day 14 distribution in clinical status was similar between arms (P = 0.14).
	Secondary Outcomes:
	• Time to clinical improvement was similar between arms (10 days in 5-day arm vs. 11 days in 10-day arm).
	• Median duration of hospitalization for patients who were discharged on or before Day 14 was similar between arms (7 days in 5-day arm vs. 8 days in 10-day arm).
		Key Limitations:
		• Open-label trial
		• Baseline imbalances in clinical status of patients in 5-day and 10-day arms
		Interpretation:
		• In hospitalized patients with severe COVID-19 who were not receiving MV or ECMO, using RDV for 5 or 10 days had similar clinical benefits.

Key: ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CQ = chloroquine; CrCl = creatinine clearance; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal

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Chloroquine or Hydroxychloroquine and/or Azithromycin

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Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria.

Both chloroquine and hydroxychloroquine increase the endosomal pH, which inhibits fusion between SARS-CoV-2 and the host cell membrane.[1] Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 (ACE2) receptor, which may interfere with the binding of SARS-CoV to the cell receptor.[2] In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.[3] Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesized to be another potential mechanism of action for the treatment of COVID-19. Azithromycin has antiviral and anti-inflammatory properties. When used in combination with hydroxychloroquine, it has been shown to have a synergistic effect on SARS-CoV-2 in vitro and in molecular modeling studies.[4,5] However, despite demonstrating antiviral activity in some in vitro systems, neither hydroxychloroquine plus azithromycin nor hydroxychloroquine alone reduced upper or lower respiratory tract viral loads or demonstrated clinical efficacy in a rhesus macaque model.[6]

The safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin and azithromycin alone have been evaluated in randomized clinical trials, observational studies, and/or single-arm studies. Please see Table 2b for more information.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIIa)**.

Rationale

Hospitalized Patients

In a large randomized controlled platform trial of hospitalized patients in the United Kingdom (RECOVERY), hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Patients who were randomized to receive hydroxychloroquine had a longer median hospital stay than those who received the standard of care. In addition, among patients who were not on invasive mechanical ventilation at the time of randomization, those who received hydroxychloroquine were more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.[7]

The results from several additional large randomized controlled trials have been published; these trials have failed to show a benefit for hydroxychloroquine with or without azithromycin or azithromycin alone in hospitalized adults with COVID-19. In the Solidarity trial, an international randomized controlled platform trial that enrolled hospitalized patients with COVID-19, the hydroxychloroquine arm was halted for futility. There was no difference in in-hospital mortality between patients in the hydroxychloroquine arm and those in the control arm.[8] Similarly, PETAL, a randomized, placebo-controlled, blinded study, was stopped early for futility. In this study, there was no difference in the median scores on the COVID Outcomes Scale between patients who received hydroxychloroquine and those who received placebo.[9] Data from two additional randomized studies of hospitalized patients

with COVID-19 did not support using hydroxychloroquine plus azithromycin over hydroxychloroquine alone.[10,11] In RECOVERY, azithromycin alone (without hydroxychloroquine) did not improve survival or other clinical outcomes when compared to the usual standard of care.[12]

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19.[13-15] Please see Table 2b or the archived versions of the Guidelines for more information.

Given the lack of a benefit seen in the randomized clinical trials, the Panel **recommends against** using hydroxychloroquine or chloroquine and/or azithromycin to treat COVID-19 in hospitalized patients **(AI)**.

Nonhospitalized Patients

Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with early, asymptomatic, or mild COVID-19.[16,17] In an open-label trial, Mitja et al. randomized 307 nonhospitalized people who were recently confirmed to have COVID-19 to receive hydroxychloroquine or no antiviral treatment. Patients in the hydroxychloroquine arm received hydroxychloroquine 800 mg on Day 1 followed by 400 mg daily for an additional 6 days. The authors reported no difference in the mean reduction in SARS-CoV-2 RNA at Day 3 or the time to clinical improvement between the two arms (see Table 2b for more information). In another trial, treating patients who had asymptomatic or mild COVID-19 with hydroxychloroquine with or without azithromycin did not result in greater rates of virologic clearance (as measured by a negative polymerase chain reaction [PCR] result on Day 6).[18]

An open-label, prospective, randomized trial compared oral azithromycin 500 mg once daily for 3 days plus standard of care to standard of care alone in nonhospitalized, high-risk, older adults who had laboratory-confirmed or suspected COVID-19. No differences were observed between the arms in the primary endpoints of time to first self-reported recovery and hospitalization or death due to COVID-19. These findings remained consistent in an analysis that was restricted to participants with positive SARS-CoV-2 PCR results. The study was ultimately halted due to futility.[19] Similarly, in a preliminary report from ATOMIC-2, adding oral azithromycin 500 mg once daily to standard of care for 14 days did not reduce the risk of hospitalization or death among 292 participants with mild to moderate COVID-19.[20]

While ongoing clinical trials are still evaluating the use of chloroquine, hydroxychloroquine, and azithromycin in outpatients, the existing data suggest that it is unlikely that clinical benefits will be identified for these agents. The Panel **recommends against** the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in nonhospitalized patients **(AIIa)**.

Adverse Effects

Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine. Cardiac adverse events that have been reported in people who received hydroxychloroquine include QTc prolongation, Torsades de Pointes, ventricular arrythmia, and cardiac deaths.[21]

The use of azithromycin has also been associated with QTc prolongation,[22] and using it in combination with hydroxychloroquine has been associated with a higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19.[23,24]

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 2D6, and these drugs

are also P-glycoprotein inhibitors. Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[25]

Drug Availability

Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19. Furthermore, the FDA Emergency Use Authorization for hydroxychloroquine and chloroquine was revoked in June 2020.

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Table 2b. Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials that are evaluating CQ, HCQ, and/or AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM, CQ, and AZM for the treatment of COVID-19.[1-19] These studies have limitations that make them less definitive and informative than the studies discussed here. The Panel's summaries and interpretations of some of those studies are available in the archived versions of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Solidarity Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[20]			
Open-label randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,330)	**Key Inclusion Criteria:** • Aged ≥18 years • Received a diagnosis of COVID-19 **Key Exclusion Criteria:** • Already receiving study drug • Expected to be transferred elsewhere within 72 hours **Interventions:** • HCQ plus local SOC. Patients received a loading dose of HCQ 800 mg PO at entry, then HCQ 800 mg PO 6 hours later followed by a daily dose of HCQ 400 mg PO twice daily for 10 days, starting 12 hours after the entry dose. • Local SOC alone	**Number of Participants:** • ITT analysis: HCQ (n = 947) and HCQ control (n = 906) • Enrollment occurred between March 22 and October 4, 2020. **Participant Characteristics:** • 35% of patients enrolled in each arm were aged <50 years; 21% of patients were aged ≥70 years. • 21% to 23% of patients had diabetes mellitus, 20% to 21% had heart disease, and 6.5% to 7% had chronic lung disease. • At entry, 36% to 38% of patients were not on supplemental oxygen, 53% to 55% were receiving supplemental oxygen only, and 9% were receiving IMV. • SOC included corticosteroids for 23% of patients in HCQ arm and 22% of patients in SOC only arm. **Outcomes:** • No significant difference in in-hospital mortality; 104 patients (10.2%) in HCQ arm and 84 patients (8.9%) in SOC arm died by Day 28 (rate ratio 1.19; 95% CI, 0.89–1.59; *P* = 0.23).	**Key Limitations:** • Not blinded • Disease severity varied widely among patients. **Interpretation:** • HCQ does not decrease in-hospital mortality in hospitalized patients with COVID-19 when compared to SOC. • HCQ does not decrease the need for mechanical ventilation when compared to SOC. • There was no evidence of harm in the HCQ arm.

Study Design	Methods	Results	Limitations and Interpretation
Solidarity Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[20], continued			
	Primary Endpoint: • In-hospital mortality (i.e., death during the original hospitalization; follow-up ended at discharge from the hospital)	• Subgroup analyses based on age or respiratory support at entry reported no significant difference in mortality between the arms. • No difference between the arms in the secondary outcome of initiation of ventilation, and no difference in the composite outcome of in-hospital mortality or initiation of ventilation • The number of deaths due to any cardiac cause during the 14 days after enrollment (the dosing period) was lower in these 2 arms than in the other study arms (the RDV, LPV/RTV, and IFN arms and their respective control arms).	
PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21]			
Randomized, placebo-controlled, blinded trial in hospitalized adults (n = 479)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Symptoms of respiratory illness for <10 days **Key Exclusion Criteria:** • More than 1 dose of HCQ or CQ during the previous 10 days • Prolonged QTc interval (>500 ms) **Interventions:** • HCQ 400 mg PO twice daily for 2 doses, then HCQ 200 mg PO twice daily for 8 doses • Matching placebo **Primary Endpoint:** • Clinical status 14 days after randomization, as measured by a 7-point ordinal scale (the COVID Outcomes Scale)	**Number of Participants:** • Enrollment occurred between April 2 and June 19, 2020. • HCQ (n = 242) and placebo (n = 237) • Planned sample size was 510 participants, but study enrollment was halted early due to futility. **Participant Characteristics:** • Median age was 58 and 57 years in HCQ and placebo arms, respectively; 33% of patients were aged ≥65 years and 24% of patients were Black/African American. • 33% to 36% of patients had diabetes mellitus, 6% to 12% had heart disease, and 7% to 9% had chronic lung disease. • At randomization, 5.4% of patients in HCQ arm and 8% in placebo arm were receiving IMV or ECMO. In both arms, 11% to 12% of patients were receiving noninvasive ventilation or HFNC oxygen, 46% to 48% were receiving low-flow oxygen, and 35% were receiving no respiratory support. • Among the patients who received concomitant medications, 22% received RDV, 19% received AZM, and 18% received corticosteroids. There was no difference in concomitant medication use between the arms.	**Key Limitations:** • It is unclear how the primary outcome of this study (a median COVID Outcomes Scale score) translates to clinical practice. **Interpretation:** • HCQ does not improve patient scores on the COVID Outcomes Scale in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection when compared to placebo. • HCQ did not improve survival or time to discharge in these patients when compared to placebo.

Study Design	Methods	Results	Limitations and Interpretation
PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21], continued			
		Outcomes: • Median COVID Outcomes Scale score was 6 in HCQ arm (IQR 4–7) and 6 in placebo arm (IQR 4–7; aOR 1.02; 95% CI, 0.73–1.42). • No difference between the arms in the secondary outcome of all-cause, all-location death at Day 14 and Day 28 • No difference between the arms in the number of any of the following systematically collected safety events: cardiac arrest treated with CPR, symptomatic hypoglycemia, ventricular arrhythmia, or seizure • Among patients who had QTc assessed, 5.9% in HCQ arm and 3.3% in placebo arm had a recorded QTc interval >500 ms during the first 5 days of dosing.	
RECOVERY Trial[22]			
Open-label, randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,197)	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Patients with prolonged QTc intervals were excluded from HCQ arm. **Interventions:** • HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge • Usual SOC **Primary Endpoint:** • All-cause mortality at Day 28 after randomization	**Number of Participants:** • HCQ (n = 1,561) and SOC (n = 3,155) • Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ. **Participant Characteristics:** • Mean age was 65 years in both arms; 41% of patients were aged ≥70 years. • 90% of patients had laboratory-confirmed SARS-CoV-2 infection. • 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. • At randomization, 17% of patients were receiving IMV or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. • Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone.	**Key Limitations:** • Not blinded • Information on occurrence of new major cardiac arrythmia was not collected throughout the trial. **Interpretation:** • HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. • Patients who received HCQ had a longer median length of hospital stay, and those who were not on IMV at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial[22], continued			
		Outcomes: • No significant difference in 28-day mortality between the 2 arms; 421 patients (26.8%) in HCQ arm and 790 patients (27.0%) in SOC arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.97–1.23; *P* = 0.15). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,266 participants (90.5%) who had a positive SARS-CoV-2 test result. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ and who were not on IMV at baseline had an increased risk of requiring intubation and an increased risk of death. • At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 735 patients (47.1%) in HCQ arm and 1,421 patients (45.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention; 1 case of Torsades de Pointes was reported in HCQ arm.	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23]			
Open-label, 3-arm RCT in hospitalized adults (n = 667)	**Key Inclusion Criteria:** • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days	**Number of Participants:** • mITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). **Participant Characteristics:** • Mean age was 50 years. • 58% of patients were men.	**Key Limitations:** • Not blinded • Follow-up period was restricted to 15 days. **Interpretation:** • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23], continued			
	Key Exclusion Criteria: • Need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask • History of ventricular tachycardia • QT interval ≥480 ms **Interventions:** • HCQ 400 mg twice daily for 7 days plus SOC • HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC • SOC alone **Primary Endpoint:** • Clinical status at Day 15, as measured by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection **Ordinal Scale Definitions:** 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, not on oxygen 4. Hospitalized, on oxygen 5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation 6. Hospitalized, on mechanical ventilation 7. Death	• At baseline, 58.2% of patients were Ordinal Level 3; 41.8% were Ordinal Level 4. • Median time from symptom onset to randomization was 7 days. • 23.3% to 23.9% of patients received oseltamivir. **Outcomes:** • No significant difference in the odds of worse clinical status at Day 15 between patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$) • No significant differences in secondary outcomes of the 3 arms, including progression to mechanical ventilation during the first 15 days and mean number of days "alive and free of respiratory support" • A greater proportion of patients in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). • QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period.	with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19[24]			
Randomized, placebo-controlled trial in nonhospitalized adults (n = 491)	**Key Inclusion Criteria:** • Symptoms that were compatible with COVID-19 and lasted ≤4 days • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days **Key Exclusion Criteria:** • Aged <18 years • Hospitalized • Receipt of certain medications **Interventions:** • HCQ 800 mg once, then HCQ 600 mg in 6–8 hours, then HCQ 600 mg once daily for 4 days • Placebo **Primary Endpoints:** • Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. • Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, measured by a 10-point, self-reported, visual analogue scale	**Number of Participants:** • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) **Participant Characteristics:** • 241 patients were exposed to people with COVID-19 through their position as health care workers (57%), 106 were exposed through household contacts (25%), and 76 had other types of exposure (18%). • Median age was 40 years. • 56% of patients were women. • Only 3% of patients were Black. • Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions. • 56% of patients were enrolled on Day 1 of symptom onset. • 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact. **Outcomes:** • Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$). • Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). • No difference in the incidence of hospitalization between the arms (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19 • A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$).	**Key Limitations:** • This study enrolled a highly heterogeneous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms. • This study used surveys for screening, symptom assessment, and adherence reporting. • Visual analogue scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated. **Interpretation:** • The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Mild COVID-19[25]			
Open-label RCT in nonhospitalized adults (n = 353)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • <5 days of mild COVID-19 symptoms **Key Exclusion Criteria:** • Moderate to severe COVID-19 • Severe liver or renal disease • History of cardiac arrhythmia • QT prolongation **Interventions:** • HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days • No antiviral treatment (control arm) **Primary Endpoint:** • Reduction in SARS-CoV-2 viral load, assessed using NP swabs on Days 3 and 7 **Secondary Endpoints:** • Disease progression up to Day 28 • Time to complete resolution of symptoms	**Number of Participants:** • ITT analysis: HCQ (n = 136) and control (n = 157) • 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. **Participant Characteristics:** • Mean age was 41.6 years. • 67% of patients were woman. • Majority of patients were health care workers (87%). • 53% of patients reported chronic health conditions. • Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). • Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss. **Outcomes:** • No significant difference in viral load reduction between control arm and HCQ arm at Day 3 • (-1.41 vs. -1.41 $\log_{10}$ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 log10 copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29). • No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77) • No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; $P = 0.38$) • A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and "nervous system disorders." • SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in HCQ arm were not deemed to be related to the drug.	**Key Limitations:** • Open-label, non-placebo-controlled trial • Study design allowed for the possibility of dropouts in control arm and over-reporting of AEs in HCQ arm. • The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. • The majority of the participants were relatively young health care workers. **Interpretation:** • Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin[26]			
Retrospective, multicenter, observational study in a random sample of hospitalized adults with COVID-19 from the New York Department of Health (n = 1,438)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ plus AZM • HCQ alone • AZM alone • Neither drug **Primary Endpoint:** • In-hospital mortality **Secondary Endpoint:** • Cardiac arrest and arrhythmia or QT prolongation on an ECG	**Number of Participants:** • HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) Participant Characteristics: • Patients in the treatment arms had more severe disease at baseline than those who received neither drug. **Outcomes:** • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug. • Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).	**Key Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City[27]			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department **Interventions:** • HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days • No HCQ **Primary Endpoint:** • Time from study baseline (24 hours after patients arrived at the ED) to intubation or death	**Number of Participants:** • Received HCQ (n = 811) and did not receive HCQ (n = 565) **Participant Characteristics:** • HCQ recipients were more severely ill at baseline than those who did not receive HCQ. **Outcomes:** • Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). • No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31)	**Key Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Key: AE = adverse event; AV = atrioventricular; AZM = azithromycin; CPR = cardiopulmonary resuscitation; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = emergency department, FiO_2 = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; IFN = interferon; IMV = invasive mechanical ventilation; ITT = intention-to-treat; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care

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Interferons

Last Updated: December 16, 2021

Interferons are a family of cytokines with in vitro and in vivo antiviral properties. Interferon beta-1a has been approved by the Food and Drug Administration (FDA) to treat relapsing forms of multiple sclerosis, and it has been evaluated in clinical trials for the treatment of COVID-19. Interferon alfa has been approved to treat hepatitis B and hepatitis C virus infections, and interferon lambda is not currently approved by the FDA for any use. Both interferon alfa and lambda have also been evaluated for the treatment of COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **systemic interferon beta** for the treatment of hospitalized patients with COVID-19 **(AI)**.
- The Panel **recommends against** the use of **interferon alfa** or **lambda** for the treatment of hospitalized patients with COVID-19, except in a clinical trial **(AIIa)**.
- The Panel **recommends against** the use of **interferons** for the treatment of nonhospitalized patients with mild or moderate COVID-19, except in a clinical trial **(AIIa)**.

Rationale

Many of the early studies that evaluated the use of systemic interferons for the treatment of COVID-19 were conducted in early 2020, before the widespread use of remdesivir and corticosteroids. In addition, these early studies administered interferons with other drugs that have since been shown to have no clinical benefit in people with COVID-19, such as lopinavir/ritonavir and hydroxychloroquine.[1-3]

More recent studies have not demonstrated efficacy for interferons in the treatment of COVID-19, and some of the trials suggested potential harm in patients with severe disease, such as those who were on high-flow oxygen, noninvasive ventilation, or mechanical ventilation.[4,5] In a large randomized controlled trial of hospitalized patients with COVID-19, the combination of interferon beta-1a plus remdesivir showed no clinical benefit when compared to remdesivir alone.[4] Similarly, the World Health Organization Solidarity trial did not show a benefit for interferon beta-1a when this drug was administered to hospitalized patients, approximately 50% of whom were on corticosteroids.[5]

Other interferons, including systemic interferon alfa or lambda and inhaled interferons, have also been evaluated in patients with COVID-19; however, these interferons (with the exception of subcutaneous interferon alfa) are not available in the United States. The trials that have evaluated interferon alfa and interferon lambda have generally been small or moderate in size and have not been adequately powered to assess whether these agents provide a clinical benefit for patients with COVID-19 (see Table 2c).

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of interferons for the treatment of COVID-19.

Adverse Effects

The most frequent adverse effects of systemic interferon include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression, suicidal ideation). Interferon beta is better tolerated than interferon alfa, but it can cause similar types of adverse effects.[6,7]

Drug-Drug Interactions

Additive toxicities may occur when systemic interferons are used concomitantly with other immunomodulators and chemotherapeutic agents.[6,7]

Considerations in Pregnancy

According to analyses of data from several large pregnancy registries, exposure to interferon beta-1b prior to conception or during pregnancy does not lead to an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly).[8,9] Exposure to interferon beta-1b did not influence birth weight, height, or head circumference.[10]

Considerations in Children

There are currently not enough data on the use of interferons to treat respiratory viral infections in children to make any recommendations for treating children with COVID-19.

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Table 2c. Interferons: Selected Clinical Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for interferons. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTT-3: Multinational, Double-Blind RCT of Interferon Beta-1a and Remdesivir in Hospitalized Adults With COVID-19[1]		

Key Inclusion Criteria:
• Evidence of pneumonia (radiographic infiltrates, SpO_2 ≤94% on room air, or supplemental oxygen)
• No MV required
Key Exclusion Criteria:
• AST or ALT >5 times ULN
• Impaired renal function
• Anticipated hospital discharge or transfer within 72 hours
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus IFN beta-1a 44 µg SQ every other day for up to 4 doses (n = 487)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus placebo (n = 482)
Primary Endpoint:
• Time to recovery by Day 28
Key Secondary Endpoints:
• Clinical status at Day 14, as measured by an OS
• Mortality by Day 28
	Participant Characteristics:
	• Mean age 59 years; 38% were aged ≥65 years
	• 58% men; 32% Latino, 60% White, 17% Black
	• Mean of 8.6 days of symptoms before enrollment
	• 90% had ≥1 comorbidity; 58% with HTN; 58% with obesity; 37% with DM
	Primary Outcome:
	• Median time to recovery for both arms was 5 days (rate ratio 0.99; 95% CI, 0.87–1.13; *P* = 0.88).
	  • In patients on high-flow oxygen or NIV (OS6) at baseline, median time to recovery was >28 days in IFN beta-1a arm and 9 days in placebo arm (rate ratio 0.40; 95% CI, 0.22–0.75; *P* = 0.0031).
	Secondary Outcomes:
	• No difference between arms in clinical improvement at 14 days (OR 1.01; 95% CI, 0.79–1.28).
	• No difference between arms in mortality by Day 28 in:
	  • All patients: 5% vs. 3% (HR 1.33; 95% CI, 0.69–2.55)
	  • Patients with OS6 at baseline: 21% vs. 12% (HR 1.74; 95% CI, 0.51–5.93)
		Key Limitation:
		• OS6 patients were excluded after 270 patients were enrolled because of an increased frequency of AEs in this group
		Interpretation:
		• There was no clinical benefit of IFN beta-1a plus RDV in hospitalized patients compared to RDV alone.
		• The use of IFN beta-1a was associated with worse outcomes among patients who were OS6 at baseline.

Methods	Results	Limitations and Interpretation
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of IV or SQ Interferon Beta-1a or Other Repurposed Drugs in Hospitalized Adults With COVID-19[2]		
Key Inclusion Criteria: • Diagnosis of COVID-19 • Not expected to be transferred elsewhere within 72 hours **Interventions:** • IFN beta-1a 44 µg SQ on day of randomization, Day 3, and Day 6 (n = 1,656) • IFN beta-1a 10 µg IV daily for 6 days for patients on high-flow oxygen, ventilation, or ECMO (n = 394) • IFN beta-1a (either SQ or IV) and LPV/RTV 400 mg/50 mg twice daily for 14 days (n = 651) • Local SOC (n = 2,050) **Primary Endpoint:** • In-hospital mortality **Key Secondary Endpoint:** • Initiation of ventilation	**Participant Characteristics:** • 35% aged <50 years; 19% aged ≥70 years; 63% men • 70% on supplemental oxygen; 7% on ventilation • Approximately 50% received corticosteroids during the study **Primary Outcome:** • In-hospital mortality was 11.9% for combined IFN beta-1a arms and 10.5% in SOC arm (rate ratio 1.16; 95% CI, 0.96–1.39). • For IFN beta-1a only (without LPV/RTV) recipients vs. SOC recipients, rate ratio was 1.12 (95% CI, 0.83–1.51). • Among those on ventilation at entry, age-stratified rate ratio for in-hospital mortality was 1.40 (95% CI, 0.93–2.11). **Secondary Outcome:** • 10% initiated ventilation in the combined IFN beta-1a arms and SOC arm.	**Key Limitations:** • Open-label study • IFN beta-1a given as IV or SQ formulations at different doses **Interpretation:** • IFN beta-1a does not improve mortality for hospitalized patients.

Methods	Results	Limitations and Interpretation
DisCoVeRy Solidarity Trial Add-On: Open-Label, Adaptive RCT of SQ Interferon Beta-1a Plus Lopinavir/Ritonavir, Lopinavir/Ritonavir, or Hydroxychloroquine in Hospitalized Adults With COVID-19 in France[3]		

Key Inclusion Criteria:
• Positive PCR result for SARS-CoV-2
• Patients had pulmonary rales or crackles with SpO_2 ≤94% or they required supplemental oxygen
Interventions:
• IFN beta-1a 44 ug SQ on Days 1, 3, and 6 plus LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• HCQ 400 mg twice on Day 1, then HCQ 400 mg daily for 9 days plus SOC (n = 145)
• SOC alone, which included corticosteroids, anticoagulants, or immunomodulatory agents but not antivirals (n = 148)
Primary Endpoint:
• Clinical status at Day 15, as measured by an OS
Key Secondary Endpoints:
• Clinical status at Day 29
• Rate of SARS-CoV-2 viral clearance
• Time to SARS-CoV-2 viral clearance
• Time to improvement of 2 OS categories
• Time to hospital discharge
	Participant Characteristics:
	• Median age 63 years; 72% men
	• 29% were obese; 26% with chronic cardiac disease; 22% with DM
	• 36% had severe disease
	• Median of 9 days from symptom onset to randomization
	• 30% received steroids during the study
	Primary Outcome:
	• No difference in clinical status at Day 15 for any intervention compared to SOC:
	  • IFN beta-1a plus LPV/RTV: aOR 0.69 (95% CI, 0.45–1.04; *P* = 0.08)
	  • LPV/RTV: aOR 0.83 (95% CI, 0.55–1.26; *P* = 0.39)
	  • HCQ: aOR 0.93 (95% CI, 0.62–1.41; *P* = 0.75)
	Secondary Outcomes:
	• No difference in clinical status at Day 29 between the arms.
	• No difference in rate and time to SARS-CoV-2 viral clearance between the arms.
	• Time to 2 OS-category improvement and hospital discharge by Day 29 was longer in LPV/RTV plus IFN beta-1a and LPV/RTV arms than in SOC arm.
		Key Limitations:
		• Open-label study
		• Most patients had moderate disease
		• No IFN beta-1a arm without LPV/RTV
		• Study stopped early for futility
		Interpretation:
		• Compared to SOC alone, the use of IFN-beta-1a plus LPV/RTV did not improve clinical status, rate of viral clearance, or time to viral clearance in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
Single-Blind RCT of Peginterferon Lambda-1a for Treatment of Outpatients With Uncomplicated COVID-19 in the United States[4]		

Key Inclusion Criteria:
• Aged 18–65 years
• Asymptomatic or symptomatic
• Positive RT-PCR result for SARS-CoV-2 within 72 hours of enrollment
Key Exclusion Criteria:
• Current or imminent hospitalization
• Respiratory rate >20 breaths/min
• SpO_2 <94% on room air
• Decompensated liver disease
Interventions:
• Single dose of PEG-IFN lambda-1a 180 µg SQ (n = 60)
• Placebo (n = 60)
Primary Endpoint:
• Time to first negative SARS-CoV-2 RT-PCR result
Key Secondary Endpoints:
• Hospitalizations by Day 28
• Time to complete symptom resolution
	Participant Characteristics:
	• Median age 36 years; 42% women; 63% Latinx, 28% White
	• 7% were asymptomatic
	• Median of 5 days of symptoms before randomization
	Primary Outcome:
	• Median time to cessation of viral shedding was 7 days in both arms (aHR 0.81; 95% CI, 0.56–1.19; *P* = 0.29).
	Secondary Outcomes:
	• No difference between PEG-IFN lambda-1a and placebo arms in:
	  • Proportion of patients hospitalized by Day 28: 3.3% for each arm
	  • Time to resolution of symptoms: 8 days vs. 9 days (HR 0.94; 95% CI, 0.64–1.39)
	Other Outcomes:
	• Patients who received PEG-IFN lambda-1a were more likely to have transaminase elevations than patients who received placebo (25% vs. 8%; *P* = 0.027).
		Key Limitation:
		• Small sample size
		Interpretation:
		• PEG-IFN lambda-1a provided no virologic or clinical benefit compared to placebo among outpatients with uncomplicated COVID-19.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Peginterferon Lambda in Outpatients With Laboratory-Confirmed COVID-19 in Canada[5]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR result • Patients were within 7 days of symptom onset, or, if asymptomatic, were within 7 days of first positive SARS-CoV-2 test result **Key Exclusion Criterion:** • Immunosuppression or condition that could be worsened by PEG-IFN lambda **Interventions:** • Single dose of PEG-IFN lambda 180 µg SQ (n = 30) • Placebo (n = 30) **Primary Endpoint:** • Proportion of participants with negative nasal mid-turbinate swab for SARS-CoV-2 at Day 7 **Key Secondary Endpoints:** • Quantitative change in SARS-CoV-2 RNA over time • Hospitalizations by Day 14	**Participant Characteristics:** • Median age 46 years; 58% women; 52% White • 19% were asymptomatic • Mean of 4.5 days of symptoms before randomization **Primary Outcome:** • 80% in PEG-IFN lambda arm and 63% in placebo arms were negative for SARS-CoV-2 RNA at Day 7 ($P = 0.15$). **Secondary Outcomes:** • VL decline by Day 7 was greater in PEG-IFN lambda arm than in placebo arm ($P = 0.0041$). • 1 participant in each arm was admitted to the hospital by Day 14. **Other Outcomes:** • 3 participants in each arm had mild elevation of aminotransferase concentrations. Increase was greater in PEG-IFN lambda arm.	**Key Limitation:** • Small sample size **Interpretation:** • PEG-IFN lambda may accelerate VL decline and clearance in outpatients with COVID-19; however, the clinical significance of this finding is unclear.

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HCQ = hydroxychloroquine; HTN = hypertension; IFN = interferon; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SQ = subcutaneous; ULN = upper limit of normal; VL = viral load

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Ivermectin

Last Updated: February 11, 2021

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.[1] It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock.[2] For these indications, ivermectin has been widely used and is generally well tolerated.[1,3] Ivermectin is not approved by the FDA for the treatment of any viral infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.[4,5] In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[6] Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.[4,7-9] Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[10-12]

Some observational cohorts and clinical trials have evaluated the use of ivermectin for the prevention and treatment of COVID-19. Data from some of these studies can be found in Table 2d.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Rationale

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures.[13] However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.[14,15] Even though ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 in vitro.[16-19] Subcutaneous administration of ivermectin 400 μg/kg had no effect on SARS-CoV-2 viral loads in hamsters. However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.[20]

Since the last revision of this section of the Guidelines, the results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Some clinical studies showed no benefits or worsening of disease after ivermectin use,[21-24] whereas others reported shorter time to resolution of disease manifestations that were attributed to COVID-19,[25-27] greater reduction in inflammatory marker levels,[26] shorter time to viral clearance,[21] or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.[21,27]

However, most of these studies had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. These limitations include:

- The sample size of most of the trials was small.
- Various doses and schedules of ivermectin were used.
- Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.
- Patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids) in addition to ivermectin or the comparator drug. This confounded the assessment of the efficacy or safety of ivermectin.
- The severity of COVID-19 in the study participants was not always well described.
- The study outcome measures were not always clearly defined.

Table 2d includes summaries of key studies. Because most of these studies have significant limitations, the Panel cannot draw definitive conclusions on the clinical efficacy of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of ivermectin in the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.[28]
- Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.
- The FDA issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans.
- Please see Table 2d for additional information.

Considerations in Pregnancy

In animal studies, ivermectin was shown to be teratogenic when given in doses that were maternotoxic. These results raise concerns about administering ivermectin to people who are in the early stages of pregnancy (prior to 10 weeks gestation).[29] A 2020 systematic review and meta-analysis reviewed the incidence of poor maternal and fetal outcomes after ivermectin was used for its antiparasitic properties during pregnancy. However, the study was unable to establish a causal relationship between ivermectin use and poor maternal or fetal outcomes due to the quality of evidence. There are numerous reports of inadvertent ivermectin use in early pregnancy without apparent adverse effects.[30-32] Therefore, there is insufficient evidence to establish the safety of using ivermectin in pregnant people, especially those in the later stages of pregnancy.

One study reported that the ivermectin concentrations secreted in breastmilk after a single oral dose were relatively low. No studies have evaluated the ivermectin concentrations in breastmilk in patients who received multiple doses.

Considerations in Children

Ivermectin is used in children weighing >15 kg for the treatment of helminthic infections, pediculosis, and scabies. The safety of using ivermectin in children weighing <15 kg has not been well established. Ivermectin is generally well tolerated in children, with a side effect profile similar to the one seen in adults. Currently, there are no available pediatric data from clinical trials to inform the use of ivermectin for the treatment or prevention of COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of ivermectin for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.

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Table 2d. Ivermectin: Selected Clinical Data

Last Updated: December 16, 2021

The Panel has reviewed other clinical studies of IVM for the treatment of COVID-19.[1-26] However, those studies have limitations that make them less definitive and informative than the studies discussed below. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
IVERCOR-COVID19: Double-Blind, Placebo-Controlled RCT of Ivermectin to Prevent Hospitalizations in Patients With COVID-19 in Argentina[27]		
Key Inclusion Criterion: • Positive SARS-CoV-2 RT-PCR result within 48 hours of screening **Key Exclusion Criteria:** • Oxygen supplementation or hospitalization • Concomitant use of CQ or HCQ **Interventions:** • Weight-based doses of IVM given at enrollment and 24 hours later for a maximum total dose of 48 mg (n = 250) • Placebo (n = 251) **Primary Endpoint:** • Hospitalization for any reason **Key Secondary Endpoints:** • Need for MV • All-cause mortality	**Participant Characteristics:** • Mean age 42 years; 8% aged ≥65 years • 47% were women • 24% with HTN; 10% with DM; 58% with ≥1 comorbidity • Median time from symptom onset was 4 days **Primary Outcome:** • COVID-19-related hospitalizations: 5.6% in IVM arm vs. 8.3% in placebo arm (OR 0.65; 95% CI, 0.32–1.31; P = 0.23) **Secondary Outcomes:** • Need for MV: 2% in IVM arm vs. 1% in placebo arm (P = 0.7) • All-cause deaths: 2% in IVM arm vs. 1% in placebo arm (P = 0.7) • AEs: 18% in IVM arm vs. 21% in placebo arm (P = 0.6)	**Key Limitation:** • Study enrolled a fairly young population with few comorbidities that predict disease progression **Interpretation:** • In patients who had recently acquired SARS-CoV-2 infection, there was no evidence of a clinical benefit for IVM.

Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild COVID-19 in Columbia[28]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR or antigen test result • Symptoms for ≤7 days • Mild disease **Key Exclusion Criteria:** • Asymptomatic disease • Severe pneumonia • Hepatic dysfunction **Interventions:** • IVM 300 µg/kg per day for 5 days (n = 200) • Placebo (n = 198) **Primary Endpoint:** • Time to resolution of symptoms within 21 days **Key Secondary Endpoints:** • Proportion of patients with clinical deterioration • Proportion of patients who required escalation in care	**Participant Characteristics:** • Median age 37 years; 4% in IVM arm and 8% in placebo arm aged ≥65 years • 39% in IVM arm and 45% in placebo arm were men • 79% had no known comorbidities • Median of 5 days from symptom onset to randomization **Primary Outcomes:** • Median time to symptom resolution: 10 days in IVM arm vs. 12 days in placebo arm (HR 1.07; *P* = 0.53) • Symptoms resolved by Day 21: 82% in IVM arm vs. 79% in placebo arm **Secondary Outcomes:** • No difference between arms in proportion of patients who had clinical deterioration or who required escalation in care. **Safety Outcomes:** • Discontinued treatment due to an AE: 8% in IVM arm vs. 3% in placebo arm • No SAEs were considered to be related to study interventions.	**Key Limitations:** • Primary endpoint changed from proportion of patients with clinical deterioration to time to symptom resolution during the trial due to low event rates • Study enrolled younger, healthier patients; this population does not typically develop severe COVID-19 **Interpretation:** • A 5-day course of IVM 300 µg/kg per day did not improve the time to resolution of symptoms in patients with mild COVID-19.

Methods	Results	Limitations and Interpretation
Open-Label RCT of Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients With Mild to Moderate COVID-19 in Bangladesh[29]		
Key Inclusion Criteria: • Aged 16–80 years • PCR-confirmed SARS-CoV-2 infection • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions:** • Single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days (n = 60) • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days (n = 56) **Primary Endpoints:** • Time to negative PCR result • Time to resolution of symptoms	**Participant Characteristics:** • Mean age 34 years; 78% were men • 78% were symptomatic at baseline **Primary Outcomes:** • Mean time to negative PCR result: 9 days in both arms • In patients who were symptomatic at baseline, mean time to negative PCR result: 9 days in IVM/DOX arm vs. 10 days in HCQ/AZM arm (P = 0.07) • Mean time to symptom recovery: 6 days in IVM/DOX arm vs. 7 days in HCQ/AZM arm (P = 0.07) • Patients who received IVM/DOX had fewer AEs than those who received HCQ/AZM (32% vs. 46%).	**Key Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients who were not at high risk for disease progression **Interpretation:** • There was no difference in the time to a negative SARS-CoV-2 PCR result or symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild to Moderate COVID-19 in India[30]		
Key Inclusion Criteria: • Positive SARS-CoV-2 RT-PCR or antigen test result • Hospitalized with mild or moderate COVID-19 **Interventions:** • IVM 12 mg for 2 days (n = 55) • Placebo (n = 57) **Primary Endpoint:** • Negative SARS-CoV-2 RT-PCR result on Day 6 **Key Secondary Endpoints:** • Symptom resolution by Day 6 • Discharge by Day 10 • Need for ICU admission or MV • Mortality	**Participant Characteristics:** • Mean age 53 years; 28% were women • 35% with HTN; 36% with DM • 79% with mild COVID-19 • Mean of 6.9 days from symptom onset • 100% received HCQ, steroids, and antibiotics; 21% received RDV; 6% received tocilizumab **Primary Outcome:** • Negative RT-PCR result on Day 6: 24% in IVM arm vs. 32% in placebo arm (rate ratio 0.8; P = 0.348) **Secondary Outcomes:** • Symptom resolution by Day 6: 84% in IVM arm vs. 90% in placebo arm (rate ratio 0.9; P = 0.36)	**Key Limitations:** • The primary endpoint of the study was a negative SARS-CoV-2 RT-PCR result on Day 6. However, the study reported no RT-PCR result or an inconclusive RT-PCR result for 42% of patients in the IVM arm and 23% in the placebo arm. • Time to discharge was not reported and outcomes after discharge were not evaluated **Interpretation:** • There was no significant virologic or clinical benefit of IVM for patients with mild to moderate COVID-19.

Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild to Moderate COVID-19 in India[30], continued		
	• Discharge by Day 10: 80% in IVM arm vs. 74% in placebo arm (RR 1.1; *P* = 0.43) • No difference between arms in proportion of patients who were admitted to ICU or who required MV. • Inpatient deaths: 0 in IVM arm (0%) vs. 4 in placebo arm (7%)	
RIVET-COV : Double-Blind, Placebo-Controlled RCT of Ivermectin in Patients With Mild to Moderate COVID-19 in India[31]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR or antigen test result • Nonsevere COVID-19 **Key Exclusion Criteria:** • CrCl <30 mL/min • Transaminases >5 times ULN • MI, heart failure, QTc interval prolongation • Severe comorbidity **Interventions:** • Single dose of IVM 24 mg (n = 51) • Single dose of IVM 12 mg (n = 49) • Placebo (n = 52) **Primary Endpoints:** • Reduction of SARS-CoV-2 VL at Day 5 • Negative PCR result at Day 5 **Key Secondary Endpoints:** • Time to symptom resolution • Clinical status at Day 14 • Number of hospital-free days at Day 28	**Participant Characteristics:** • Mean age 35 years; 89% were men • 60% to 68% had mild COVID-19 (including asymptomatic patients); 33% to 40% had moderate COVID-19 • Median duration of symptoms was similar between arms (4–5 days). • 10% received concurrent antivirals (RDV, favipiravir, or HCQ); no difference between arms. **Primary Outcomes:** • Proportion with negative PCR result on Day 5: 48% in IVM 24 mg arm vs. 35% in IVM 12 mg arm vs. 31% in placebo arm (*P* = 0.30) • VL at enrollment did not impact conversion to negative RT-PCR on Day 5. • No significant difference between arms in VL decline by Day 5. **Secondary Outcomes:** • No difference between arms in time to symptom resolution or number of hospital-free days at Day 28. • Proportion with clinical worsening similar across arms: 8% in IVM 24 mg arm vs. 5% in IVM 12 mg arm vs. 11% in placebo arm (*P* = 0.65) • No difference between arms in frequency of AEs. • No SAEs reported.	**Key Limitation:** • Small sample size **Interpretation:** • There was no difference in the rate of negative PCR results on Day 5 or clinical outcomes between patients who received IVM and those who received placebo.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Ivermectin, Chloroquine, or Hydroxychloroquine in Hospitalized Adults With Severe COVID-19 in Brazil[32]		

Key Inclusion Criteria:
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following severity criteria:
  • Dyspnea
  • Tachypnea (>30 breaths/min)
  • SpO_2 <93%
  • PaO_2/FiO_2 <300 mm Hg
  • Involvement of >50% of lungs on CXR or CT
Key Exclusion Criterion:
• Cardiac arrhythmia
Interventions:
• IVM 14 mg once daily for 3 days (n = 53)
• CQ 450 mg twice daily on Day 0, then once daily for 4 days (n = 61)
• HCQ 400 mg twice daily on Day 0, then once daily for 4 days (n = 54)
Endpoints:
• Need for supplemental oxygen, MV, or ICU admission
• Mortality
	Participant Characteristics:
	• Mean age 53 years; 58% were men
	• Most common comorbidities: HTN (43%); DM (28%); BMI >30 (38%)
	• 76% had respiratory failure on admission
	Outcomes:
	• No difference between IVM, CQ, and HCQ arms in:
	  • Proportion requiring supplemental oxygen: 88% vs. 89% vs. 90%
	  • ICU admission: 28% vs. 22% vs. 21%
	  • Need for MV: 24% vs. 21% vs. 21%
	  • Mortality: 23% vs. 21% vs. 22%
	  • Mean number of days of supplemental oxygen: 8 days for each arm
	• No difference in proportion of patients with AEs between the arms.
	• Baseline characteristics that were significantly associated with mortality:
	  • Aged >60 years (HR 2.4)
	  • DM (HR 1.9)
	  • BMI >33 (HR 2.0)
	  • SpO_2 <90% (HR 5.8)
		Key Limitations:
		• Small sample size
		• No placebo control
		• No clearly defined primary endpoint
		Interpretation:
		• Compared to CQ or HCQ, IVM did not reduce the proportion of hospitalized patients with severe COVID-19 who required supplemental oxygen, ICU admission, or MV or the proportion of patients who died.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Ivermectin as Adjunctive Therapy in Hospitalized Patients With Mild to Severe COVID-19 in Iran[33]		

Key Inclusion Criterion:
• Symptoms suggestive of COVID-19 pneumonia, with compatible chest CT scan or positive SARS-CoV-2 PCR result
Key Exclusion Criterion:
• Severe immunosuppression, malignancy, or chronic kidney disease
Interventions:
• HCQ 200 mg twice daily as SOC plus 1 of the following:
  • SOC alone (n = 30)
  • Placebo (n = 30)
  • Single dose of IVM 200 µg/kg (n = 30)
  • IVM 200 µg/kg on Days 1, 3, and 5 (n = 30)
  • Single dose of IVM 400 µg/kg (n = 30)
  • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 (n = 30)
Primary Endpoints:
• Clinical recovery
• All-cause mortality
	Participant Characteristics:
	• Median age 53–61 years across arms; 50% were men
	• Disease severity stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), severe (12%)
	• Median SpO_2 at baseline was 88% to 91% across arms
	• Proportion of patients in each arm with a positive SARS-CoV-2 PCR result varied, with a range of 47% to 97%
	Primary Outcomes:
	• Median duration of hypoxemia was shorter in IVM arms than in placebo arm ($P = 0.025$).
	• Median duration of hospitalization was shorter in IVM arms than in placebo arm ($P = 0.006$).
	• No difference between the arms in number of days of tachypnea or number of days to return to normal temperature.
	• Mortality was higher in SOC and placebo arms (18%) than in IVM arms (3%; $P < 0.001$).
		Key Limitations:
		• Since IVM was given as a single dose or multiple doses and no placebo was given to patients in these arms, the study was not truly blinded
		• Large proportion of patients did not have laboratory-confirmed SARS-CoV-2 infection, and there was an imbalance across arms in the proportion of patients with laboratory-confirmed SARS-CoV-2 infection
		• Concerns have been raised about whether the study was conducted as reported[34]
		• Post hoc grouping of randomized arms raises risk of false positive findings
		Interpretation:
		• The unclear treatment arm assignments and the lack of accounting for disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat mild COVID-19.

Key: AE = adverse event; AZM = azithromycin; BMI = body mass index; CQ = chloroquine; CrCl = creatinine clearance; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; DOX = doxycycline; HCQ = hydroxychloroquine; HTN = hypertension; ICU = intensive care unit; IVM = ivermectin; MI = myocardial infarction; MV = mechanical ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal; VL = viral load

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

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The replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.[1] Two proteases are responsible for this cleavage: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).

Lopinavir/ritonavir and darunavir/cobicistat have been studied in patients with COVID-19. The clinical trials discussed below have not demonstrated a clinical benefit for protease inhibitors in patients with COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients **(AIII)**.

Rationale

The pharmacodynamics of lopinavir/ritonavir raise concerns about whether it is possible to achieve drug concentrations that can inhibit the SARS-CoV-2 proteases.[2,3] In addition, lopinavir/ritonavir did not show efficacy in two large randomized controlled trials in hospitalized patients with COVID-19.[4,5]

There is currently a lack of data on the use of lopinavir/ritonavir in nonhospitalized patients with COVID-19. However, the pharmacodynamic concerns and the lack of evidence for a clinical benefit among hospitalized patients with COVID-19 undermine confidence that lopinavir/ritonavir has a clinical benefit at any stage of SARS-CoV-2 infection.

Adverse Events

The adverse events for lopinavir/ritonavir include:

- Nausea, vomiting, diarrhea (common)
- QTc prolongation
- Hepatotoxicity

Drug-Drug Interactions

Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A. Coadministering lopinavir/ritonavir with medications that are metabolized by this enzyme may increase the concentrations of those medications, resulting in concentration-related toxicities. Please refer to the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* for a list of potential drug interactions.

Summary of Clinical Data for COVID-19

- The plasma drug concentrations achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.[3]
- Lopinavir/ritonavir did not demonstrate a clinical benefit in hospitalized patients with COVID-19 during a large randomized trial in the United Kingdom.[4]

- In a large international randomized trial, lopinavir/ritonavir did not reduce the mortality rate among hospitalized patients with COVID-19.[5]
- A moderately sized randomized trial (n = 199) failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[6]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[7]
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Clinical Data for COVID-19 below for more information.

Clinical Data for COVID-19

The information presented in this section may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials that are evaluating lopinavir/ritonavir.

Lopinavir/Ritonavir in Hospitalized Patients With COVID-19: The RECOVERY Trial

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received lopinavir/ritonavir. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection.[4]

Patients were randomized into several parallel treatment arms; this included randomization in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours for 10 days or until hospital discharge. Patients who had severe hepatic insufficiency or who were receiving medications that had potentially serious or life-threatening interactions with lopinavir/ritonavir were excluded from randomization into either of these arms. Mechanically ventilated patients were also underrepresented in this study because it was difficult to administer the oral tablet formulation of lopinavir/ritonavir to patients who were on mechanical ventilation. The primary outcome was all-cause mortality at Day 28 after randomization.

The lopinavir/ritonavir arm was discontinued on June 29, 2020, after the independent data monitoring committee concluded that the data showed no clinical benefit for lopinavir/ritonavir.

Patient Characteristics

- Of the 7,825 participants who were eligible to receive lopinavir/ritonavir, 1,616 were randomized to receive lopinavir/ritonavir and 3,424 were randomized to receive standard of care only. The remaining participants were randomized to other treatment arms in the study.
- In both the lopinavir/ritonavir arm and the standard of care arm, the mean age was 66 years; 44% of patients were aged ≥70 years.
- Test results for SARS-CoV-2 infection were positive for 88% of patients. The remaining 12% had a negative test result.
- Comorbidities were common; 57% of patients had at least one major comorbidity. Of those patients, 28% had diabetes mellitus, 26% had heart disease, and 24% had chronic lung disease.
- At randomization, 4% of patients were receiving invasive mechanical ventilation, 70% were receiving oxygen only (with or without noninvasive ventilation), and 26% were receiving neither.
- The percentages of patients who received azithromycin or another macrolide during the follow-up

period were similar in both arms (23% in the lopinavir/ritonavir arm vs. 25% in the standard of care arm). In addition, 10% of patients in both arms received dexamethasone.

Results

- There was no significant difference in the primary outcome of 28-day mortality between the two arms; 374 patients (23%) in the lopinavir/ritonavir arm and 767 patients (22%) in the standard of care arm had died by Day 28 (rate ratio 1.03; 95% CI, 0.91–1.17; $P = 0.60$).
- A similar 28-day mortality was reported for patients who received lopinavir/ritonavir in an analysis that was restricted to the 4,423 participants who had positive SARS-CoV-2 test results (rate ratio 1.05; 95% CI, 0.92–1.19; $P = 0.49$).
- Patients in the lopinavir/ritonavir arm and patients in the standard of care arm had similar median times to discharge (11 days in both arms) and similar probabilities of being discharged alive within 28 days (69% vs. 70%).
- Among participants who were not on invasive mechanical ventilation at baseline, patients who received lopinavir/ritonavir and those who received standard of care only had similar risks of progression to intubation or death.
- Results were consistent across subgroups defined by age, sex, ethnicity, or respiratory support at baseline.

Limitations

- The study was not blinded.
- No laboratory or virologic data were collected.

Interpretation

Lopinavir/ritonavir did not decrease 28-day all-cause mortality when compared to the usual standard of care in hospitalized persons with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Participants who received lopinavir/ritonavir and those who received standard of care only had similar median lengths of hospital stay. Among the patients who were not on invasive mechanical ventilation at the time of randomization, those who received lopinavir/ritonavir were as likely to require intubation or die during hospitalization as those who received standard of care.

Lopinavir/Ritonavir in Hospitalized Patients with COVID-19: The Solidarity Trial

The Solidarity trial was an open-label, randomized controlled trial that enrolled hospitalized patients with COVID-19 in 405 hospitals across 30 countries. The study included multiple arms; in one arm, participants received lopinavir/ritonavir. The control group for this arm included people who were randomized at the same site and time who could have received lopinavir/ritonavir but received standard of care instead. Lopinavir 400 mg/ritonavir 100 mg was administered orally twice daily for 14 days or until hospital discharge. Only the oral tablet formulation of lopinavir/ritonavir was available, which precluded administration to those on mechanical ventilation. The primary outcome was in-hospital mortality.[5]

After the results of the RECOVERY trial prompted a review of the Solidarity data, the lopinavir/ritonavir arm ended enrollment on July 4, 2020. At that time, 1,411 patients had been randomized to receive lopinavir/ritonavir, and 1,380 patients received standard of care.

Patient Characteristics

- In both the lopinavir/ritonavir arm and the standard of care arm, 20% of the participants were aged ≥70 years and 37% were aged <50 years.
- Comorbidities were common. Diabetes mellitus was present in 24% of patients, heart disease in 21%, and chronic lung disease in 7%.

- At randomization, 8% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 53% were receiving oxygen only (with or without noninvasive ventilation), and 39% were receiving neither.
- Similar percentages of patients received corticosteroids in the lopinavir/ritonavir arm and the standard of care arm (23% vs. 24%). Other nonstudy treatments were administered less often, and the use of these treatments was balanced between arms.

Results

- There was no significant difference in in-hospital mortality between the two arms; 148 patients (9.7%) in the lopinavir/ritonavir arm and 146 patients (10.3%) in the standard of care arm had died by Day 28 (rate ratio 1.00; 95% CI, 0.79–1.25; $P = 0.97$).
- Progression to mechanical ventilation among those who were not ventilated at randomization occurred in 126 patients in the lopinavir/ritonavir arm and 121 patients in the standard of care arm.
- In-hospital mortality results appeared to be consistent across subgroups.

Limitations

- The study was not blinded.
- Those who were on mechanical ventilation were unable to receive lopinavir/ritonavir.
- The study includes no data on time to recovery.

Interpretation

Among hospitalized patients, lopinavir/ritonavir did not decrease in-hospital mortality or the number of patients who progressed to mechanical ventilation compared to standard of care.

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

In a case series, eight patients with COVID-19 were treated with lopinavir 400 mg/ritonavir 100 mg orally twice daily and had plasma trough levels of lopinavir drawn and assayed by liquid chromatography-tandem mass spectrometry.[3]

Results

- The median plasma lopinavir concentration was 13.6 μg/mL.
- After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the in vitro half-maximal effective concentration (EC_{50}) for SARS-CoV-2.

Limitations

- Only the trough levels of lopinavir were quantified.
- The concentration of lopinavir required to effectively inhibit SARS-CoV-2 replication in vivo is currently unknown.

Interpretation

The plasma drug concentrations that were achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.

Other Reviewed Studies

The Panel has reviewed other clinical studies that evaluated the use of protease inhibitors for the treatment of COVID-19.[6,8,9] These studies have limitations that make them less definitive and

informative than larger randomized clinical trials. The Panel's summaries and interpretations of some of these studies are available in the archived versions of the Guidelines.

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Nitazoxanide

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Nitazoxanide is a broad-spectrum thiazolide antiparasitic agent that is approved by the Food and Drug Administration (FDA) for the treatment of *Cryptosporidium parvum* and *Giardia duodenalis* infections in children aged ≥1 year and adults. Nitazoxanide is rapidly metabolized to its active metabolite, tizoxanide, and has in vitro antiviral activity against a range of viruses, including influenza viruses, hepatitis B and C viruses, norovirus, rotavirus, Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.[1-3] The mechanism of antiviral activity is not fully characterized. Nitazoxanide inhibits host enzymes, which impairs the posttranslational processing of viral proteins. It also has inhibitory effects on proinflammatory cytokines. With the exception of a Phase 2b/3 trial for uncomplicated influenza, the evidence for clinical activity of nitazoxanide against other viruses is limited or of low quality.[4]

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **nitazoxanide** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Rationale

Two randomized controlled trials that were conducted in Brazil and the United States did not find a significant clinical benefit for nitazoxanide treatment in nonhospitalized adults with COVID-19 when treatment was initiated within 2 to 5 days after illness onset.[5,6] One of these trials, which has not yet been published, reported that fewer patients in the nitazoxanide arm progressed to severe COVID-19 than in the placebo arm. However, the study was underpowered to detect a difference, and this finding was not statistically significant.[6] Additional small, unpublished studies were reviewed; however, due to their limitations, they did not provide support for the use of nitazoxanide.[7,8] Nitazoxanide was well tolerated in these trials. The Panel concluded that results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of nitazoxanide in the treatment of COVID-19.

Please see Table 2e for more information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Nitazoxanide is generally well tolerated. The most commonly reported side effects include abdominal pain, diarrhea, headache, nausea, vomiting, urine discoloration, and, rarely, ocular discoloration.
- Nitazoxanide is a highly plasma protein-bound drug (>99.9%). Drug-drug interactions may occur when nitazoxanide is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites. If nitazoxanide is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for adverse drug reactions.
- Please see Table 2f for more information.

Considerations in Pregnancy

According to the animal study data included in the product label, nitazoxanide does not appear to affect fertility, nor does it cause fetal toxicity.[9] There are no data on using nitazoxanide to treat COVID-19 in pregnant women.

Considerations in Children

Nitazoxanide is approved by the FDA for use in children aged ≥1 year old to treat *Cryptosporidium parvum* and *Giardia duodenalis* infections. Dosing for the nitazoxanide suspension or tablets is available for children that provides exposure that is similar to the approved adult dose of oral nitazoxanide 500 mg twice daily. There are no data on using nitazoxanide to treat COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of nitazoxanide for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.

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Table 2e. Nitazoxanide: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials that are evaluating NTZ for the treatment of COVID-19. The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing recommendations for NTZ.[1,2]

Study Design	Methods	Results	Limitations and Interpretation
Early Treatment of Mild COVID-19 with Nitazoxanide[3]			

Randomized, double-blind, placebo-controlled trial in nonhospitalized adults with mild COVID-19 in Brazil (n = 475)	**Key Inclusion Criteria:**
	• Clinical signs and symptoms of COVID-19 for ≤3 days (fever, dry cough, and/or fatigue)
	Key Exclusion Criteria:
	• Negative SARS-CoV-2 RT-PCR result from an NP swab
	• Renal, heart, respiratory, liver, or autoimmune diseases
	• Participant had a history of cancer in the past 5 years
	Interventions:
	• NTZ 500 mg 3 times daily for 5 days using the oral liquid formulation
	• Color-matched placebo 3 times daily for 5 days
	Primary Endpoint:
	• Complete resolution of dry cough, fever, and/or fatigue after receiving treatment for 5 days
	Key Secondary Endpoints:
	• Reduction in SARS-CoV-2 VL
	• Incidence of hospital admission after completing therapy
		Number of Participants:
		• NTZ (n = 194) and placebo (n = 198)
		Participant Characteristics:
		• Median age of patients was 37 years.
		  • Percentage of patients aged 18–39 years: 58%
		  • Percentage of patients aged 40–59 years: 36%
		  • Percentage of patients aged 60–77 years: 6%
		• 53% of patients were women.
		• 69% of patients were White.
		• 31% of patients had a BMI ≥30.
		• 85% of patients had no reported comorbidities.
		• Median time from symptom onset to first dose of study drug was 5 days (IQR 4–5 days).
		• Baseline median SARS-CoV-2 VL was 7.06 $\log_{10}$ c/mL (IQR 5.77–8.13) in NTZ arm and 7.49 $\log_{10}$ c/mL (IQR 6.15–8.32) in placebo arm (P = 0.065).
		Primary Outcome:
		• There was no difference in time to complete resolution of symptoms between NTZ and placebo arms (P = 0.277)
		Secondary Outcomes:
		• After 5 days, median SARS-CoV-2 VL was lower in NTZ arm (3.63 $\log_{10}$ c/mL [IQR 0–5.03]) than in placebo arm (4.13 $\log_{10}$ c/mL [IQR 2.88–5.31]; P = 0.006).
			Key Limitations:
			• In general, the patients in this study were young and relatively healthy.
			• At baseline, the median VL was 0.43 $\log_{10}$ c/mL lower in the NTZ arm than in the placebo arm; however, this difference was not statistically significant (trend toward a significant difference; P = 0.065). Although the difference in absolute VLs between the arms at Day 5 was reported as statistically significant, without the information on the change in VL in each arm, it is difficult to interpret the significance of the findings.
			• Some participants who received the study drug were excluded from the analysis population due to discontinued intervention (21 in NTZ arm vs. 18 in placebo arm); AEs (6 in NTZ arm vs. 1 in placebo arm); hospitalization (5 in NTZ arm vs. 5 in placebo arm); and protocol deviations (7 in NTZ arm vs. 7 in placebo arm). This complicates the interpretation of the study results, because an ITT analysis was not included.

Study Design	Methods	Results	Limitations and Interpretation
Early Treatment of Mild COVID-19 with Nitazoxanide[3], continued			
		• 29.9% of patients in NTZ arm and 18.2% of patients in placebo arm had a negative SARS-CoV-2 RT-PCR result at the fifth treatment visit ($P = 0.009$). • In the ITT study population, 5 patients on NTZ and 5 on placebo were hospitalized due to clinical deterioration; 2 who received NTZ required ICU admission vs. 0 who received placebo. These individuals were excluded from the analysis population because they did not complete the 5-day treatment course before clinical progression occurred. **Other Outcomes:** • Mild to moderate AEs occurred in about 30% of participants in each arm who completed 5 days of therapy.	**Interpretation:** • NTZ did not improve time to resolution of symptoms compared to placebo. • Median VL was lower at Day 5 in the NTZ arm than in the placebo arm, but this may reflect differences in baseline VLs. • NTZ was well tolerated.
Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide[4]			
Randomized, double-blind, placebo-controlled trial in nonhospitalized patients with COVID-19 in the United States and Puerto Rico (n = 1,092) *This is a preliminary, unpublished report that has not been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥12 years • Enrollment ≤72 hours of symptom onset • Mild to moderate COVID-19 • ≥2 respiratory symptom domains with a score ≥2 on FLU-PRO questionnaire at screening, and no improvement in overall symptom severity compared to previous day **Key Exclusion Criteria:** • Signs or symptoms of severe COVID-19 • Previous COVID-19 or any symptom suggestive of COVID-19 • Recent acute upper respiratory tract infection • Severe immunodeficiency • Severe heart, lung, neurological, or other systemic diseases	**Number of Participants:** • mITT analysis: NTZ (n = 184) and placebo (n = 195) **Participant Characteristics:** • Median age of patients was 40 years. • 43.5% of patients were men. • 87.6% of patients were White. • Median BMI was 28.9. • Median time from symptom onset to randomization was 45.9 hours. • 64.8% of patients had mild disease. • 35.2% of patients had moderate disease. • 62.8% of patients were at risk for severe illness. **Primary Outcome:** • NTZ was not associated with a reduction in median time to sustained response compared to placebo (13.3 days in NTZ arm vs. 12.4 days in placebo arm; $P = 0.88$) **Secondary Outcomes:** • Progression to severe disease occurred in 1 of 184 patients (0.5%) in NTZ arm and 7 of 195 patients (3.6%) in placebo arm ($P = 0.07$).	**Key Limitations:** • Information is limited in this preliminary report. • Because the number of high-risk participants who progressed to severe COVID-19 in this study was small, the results for this subgroup are fragile. Larger studies are needed. **Interpretation:** • NTZ did not demonstrate significant clinical or virologic benefits when compared to placebo. • NTZ was well tolerated.

Study Design	Methods	Results	Limitations and Interpretation
Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide[4], continued			
	Interventions: • 2 investigational NTZ 300 mg extended-release tablets (for a total dose of 600 mg) PO with food twice daily for 5 days • Matching placebo for 5 days • All subjects received a vitamin B complex supplement twice daily to mask potential NTZ-associated chromaturia. **Primary Endpoint:** • Time from first dose to sustained response **Secondary Endpoint:** • Rate of progression to severe COVID-19	• Among a subgroup of patients who had a high risk for severe illness according to CDC criteria, 1 of 112 patients (0.9%) in NTZ arm and 7 of 126 patients (5.6%) in placebo arm progressed to severe disease ($P = 0.07$). • 1 of 184 patients (0.5%) in NTZ arm and 5 of 195 (2.6%) in placebo arm were hospitalized ($P = 0.18$). • There was no significant difference in viral endpoints between arms at Days 4 and 10. **Other Outcomes:** • The safety analysis included 935 participants (472 in NTZ arm and 463 in placebo arm). • 2 patients in NTZ arm and 3 patients in placebo arm stopped the study drug due to AEs.	

Key: AE = adverse event; BMI = body mass index; CDC = Centers for Disease Control and Prevention; FLU-PRO = Influenza Patient Reported Outcomes; ICU = intensive care unit; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NTZ = nitazoxanide; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; RT-PCR = reverse transcription polymerase chain reaction; VL = viral load

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Table 2f. Characteristics of Antiviral Agents

Last Updated: December 16, 2021

- RDV is the only antiviral drug that is approved by the FDA for the treatment of COVID-19. Some medications that are currently being evaluated in clinical trials for the treatment of COVID-19 are also included in this table. **The inclusion of these drugs does not imply that the Panel approves of their use**.
- Information on CQ, HCQ, and LPV/RTV are available in the archived versions of the Guidelines. The Panel **recommends against** using these agents to treat COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *MedWatch* program.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the individual drug sections or Therapeutic Management of Hospitalized Adults With COVID-19.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Remdesivir *Approved by the FDA for the treatment of COVID-19 in individuals aged ≥12 years and weighing ≥40 kg.*				
Please see Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on when to use RDV. **For Hospitalized Adults and Children (Aged ≥12 Years and Weighing ≥40 kg):** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily on Days 2–5. Administer RDV IV infusion over 30–120 minutes.	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment.	• Infusion reactions • Renal function and hepatic function as clinically indicated • FDA does not recommend RDV when eGFR is <30 mL/min. See the Remdesivir section for information on using RDV in people with renal insufficiency.	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a minor substrate of CYP3A4, and a substrate of OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[1]	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • A list of clinical trials is available: Remdesivir

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir, continued				
Dose Recommended in FDA EUA For Hospitalized Children Weighing 3.5 kg to <40 kg: • RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily on Days 2–5. Administer RDV IV infusion over 30–120 minutes.	• Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD. • Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.		• No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	
Interferon Alfa *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
IFN Alfa-2b *Dose for COVID-19 in Clinical Trials:* • Nebulized IFN alfa-2b 5 million international units twice daily; the optimal duration of treatment is unclear.	• AEs that are associated with inhaled therapy (e.g., throat irritation, cough, bronchospasm) • Systemic effects of IFN are expected to be minimal.	• Respiratory symptoms after inhalation	• Low potential for drug-drug interactions	• The nebulized formulation of IFN alfa has been the formulation most commonly used in clinical trials for the treatment of COVID-19. IFN alfa is usually included as part of a combination regimen. • A list of clinical trials is available: Interferon Alfa **Availability:** • Nebulized IFN alfa-2b is not approved by the FDA for use in the United States.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferon Beta *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
IFN Beta-1a *Dose for COVID-19 in Clinical Trials:* • IFN beta-1a 44 µg SQ or IV every other day for up to 3 or 4 doses **IFN Beta-1b** *Dose for COVID-19 in Clinical Trials:* • IFN beta-1b 8 million international units SQ every other day for up to 7 days total	• Flu-like symptoms (e.g., fever, fatigue, myalgia) • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• CBC with differential • Liver enzymes • Worsening CHF • Depression, suicidal ideation	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN.	• A list of clinical trials is available: Interferon Beta **Availability** *Brand Names of IFN Beta-1a Products:* • Avonex, Plegridy, Rebif *Brand Names of IFN Beta-1b Products:* • Betaseron, Extavia
Interferon Lambda *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
PEG-IFN Lambda-1a *Dose for COVID-19 in Clinical Trials:* • Single dose of PEG-IFN lambda-1a 180 µg SQ	• Liver function abnormalities • Injection site reactions	• CBC with differential • Liver enzymes • Monitor for potential AEs.	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents.	• A list of clinical trials is available: Interferon Lambda **Availability:** • PEG-IFN lambda-1a is not approved by the FDA for use in the United States.
Ivermectin *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose for COVID-19 in Clinical Trials: • IVM 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days	• Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[2]

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Ivermectin, continued				
	parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.			• A list of clinical trials is available: Ivermectin
Nitazoxanide *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
For Adults: • Doses studied for COVID-19 range from NTZ 500 mg PO 3 times daily to 4 times daily. • Higher doses are being studied. • Doses used for antiprotozoal indications range from NTZ 500 mg–1 g PO twice daily.	• Abdominal pain • Diarrhea • Headache • Nausea • Vomiting • Urine discoloration • Ocular discoloration (rare)	• Monitor for potential AEs.	• Drug-drug interactions may occur if NTZ is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites.[3] • If NTZ is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for AEs.	• NTZ should be taken with food. • The oral suspension is not bioequivalent to the tablet formulation. • A list of clinical trials is available: Nitazoxanide

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; CQ = chloroquine; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HCQ = hydroxychloroquine; IFN = interferon; IV = intravenous; IVM = ivermectin; LPV/RTV = lopinavir/ritonavir; MATE = multidrug and toxin extrusion protein; NTZ = nitazoxanide; OATP = organic anion transporting polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; PEG-IFN = pegylated interferon; P-gp = P-glycoprotein; PO = orally; RDV = remdesivir; SBECD = sulfobutylether-beta-cyclodextrin; SQ = subcutaneous; ULN = upper limit of normal

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